Nitrosation of Phenolic Substrates under Mildly Basic Conditions: Selective Preparation of *p*-Quinone Monooximes and Their Antiviral Activities

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Received October 18, 1995[⊗]

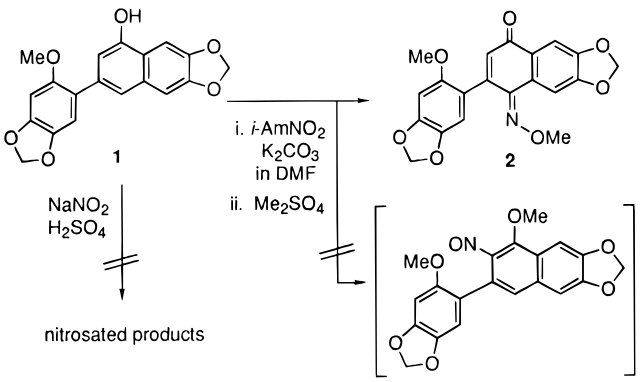
Nitrosation of 3-methoxyphenol and 1-naphthol were examined under both acidic ($NaNO_2$−$EtCO_2H$−H_2O) and basic (*i*-$AmNO_2$−K_2CO_3−DMF) conditions. Acidic nitrosations afforded *ortho*-directed products, whereas *para*-directed nitrosations were observed under basic conditions to yield *p*-quinone monooximes. The basic *para*-directed nitrosation was further examined using 15 phenols, two naphthols, and four phenolic heterocyclics. A one-pot operation of the basic nitrosation followed by methylation with dimethyl sulfate gave the corresponding methyl ethers in high yield. Two *p*-quinone monooximes derived from 3-methoxyphenol and 8-hydroxyquinoline showed a moderate activity against HSV-1, and the latter oxime was also effective against HSV-2. On the other hand, *p*-quinone monooximes derived from methyl salicylate, 1-naphthol, 7-hydroxy-2-methylbenzo[*b*]-furan, and 8-hydroxycoumarin showed the comparable activity to that of DDI against HIV-1.

Introduction

Although aromatic nitrosation[1] is restricted to only highly reactive substrates such as phenols and anilines, it is often used to directly introduce a nitrogen function into aromatics. In the usual synthetic procedure, nitrous acid is generated *in situ* by the neutralization of nitrite salts with strong (aqueous) mineral acids which also promotes the production of the active nitrosating agents. Nitrosation of phenols basically occurs at the *para* position to yield *p*-quinone monooximes,[2] unless this is blocked. However, *ortho*-nitrosation occurs in some phenols; 1-naphthol gives a mixture of 2-(*ortho*-) and 4-(*para*-) nitrosated products in a ratio of 3:2 when reacted with aqueous sodium nitrite ($NaNO_2$) in acetic acid.[3] We have found that reacting 3-aryl-1-naphthol **1** with isoamyl nitrite (*i*-$AmNO_2$) in dimethylformamide (DMF) in the presence of potassium carbonate (K_2CO_3) under nonaqueous conditions (basic nitrosation) exclusively affords a 1,4-naphthoquinone monooxime which following methylation yields the (*Z*)-ether **2**,[4] whereas nitrosation did not proceed under the usual aqueous acidic conditions (Scheme 1). Here, we present the scope and limitations of the basic nitrosation of phenolic substrates.

Synthetic aromatic nitroso compounds have antiviral activity, including that against the human immunodeficiency virus (HIV).[5] We therefore examined the antiviral activities of some nitrosated products obtained under basic conditions. Their antiviral activities against herpes simplex virus types 1 and 2 (HSV-1 and HSV-2, respectively) and HIV type 1 (HIV-1) are discussed.

Scheme 1



Results and Discussion

Basic Nitrosation. Maleski[6] has described the *ortho*-directed nitrosation of 3-methoxyphenol (**3**) in propionic acid using a limited amount of water to dissolve $NaNO_2$ to give 5-methoxy-2-nitrosophenol[2] (**4**) in 65% yield[7] as the only product. Reexamination of his method (method A) resulted in the major formation (63%) of **4** together with a small amount of an isomeric *p*-quinone monooxime **5**. The ratio of **4** to **5** was 83%. The main product was **5** (39%; 72% of the products) when **3** was subjected to basic nitrosation (method B).

We compared the nitrosation of 1-naphthol (**6**) under both conditions. The major product of method A (63%; 74% of the products) was 2-nitroso-1-naphthol (**7**),[8] whereas an isomeric 1,4-naphthoquinone 1-monooxime (**8**) was the main product (59%; 69% of the products) of method B.

These results summarized in Table 1 suggested that *ortho*- and *para*-directed nitrosation occurred in methods A and B, respectively.

To rationalize the regioselectivities of the nitrosation described above, MO calculations on protonated forms

[⊗] Abstract published in *Advance ACS Abstracts,* March 15, 1996.

(1) Coombes, R. G. In *Comprehensive Organic Chemistry*; Barton, D., Ollis W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 2, pp 305−381.

(2) It is known that *p*-nitrosated phenols exist largely as the oxime tautomer, but that *o*-nitroso derivatives exist as the nitroso tautomer, in which intramolecular hydrogen bonding is of importance.[1]

(3) Benson, W. R.; Gajan, R. J. *J. Org. Chem.* **1966**, *31*, 2498.

(4) Ishikawa, T.; Saito, S.; Ishii, H. *Tetrahedron* **1995**, *51*, 8447.

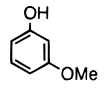
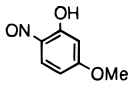
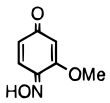
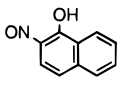
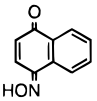
(5) Rice, W. G.; Schaeffer, C. A.; Harten, B.; Villinger, F.; South, T. L.; Summers, M. F.; Henderson, L. E.; Bess, J. W., Jr.; Arthur, L. O.; McDougal, J. S.; Orloff, S. L.; Mendeleyev, J.; Kun, E. *Nature* **1993**, *361*, 473.

(6) Maleski, R. J. *Synth. Commun.* **1993**, *23*, 343.

(7) Demonchaux *et al.* has described an alternative preparation of **4** in nearly the same yield under acidic conditions ($NaNO_2$−H_2SO_4 in H_2O). Demonchaux, P.; Lenoir, P.; Augert, G.; Dupassieux, P. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2383.

0022-3263/96/1961-2774$12.00/0

Table 1. Nitrosation of 3-Methoxyphenol (3) and 1-Naphthol (6)

run	substrate	method[a]	*o*-deriv.[b] (%)	*p*-deriv.[b] (%)	total yield[b] (%) [*o*-/*p*- ratio]
1	 **3**		 **4**	 **5**	
		A	63	13	76 [83/17]
		B	15	39	54 [28/72]
2	 **6**		 **7**[c]	 **8**	
		A	63	22	85 [74/26]
		B	26	59	85 [31/69]

[a] Method A: $NaNO_2$ in $EtCO_2H$-H_2O at -5 °C. Method B: *i*-$AmNO_2$-K_2CO_3 in DMF at rt. [b] Isolated yield. [c] Only the structure of the nitroso tautomer is given.

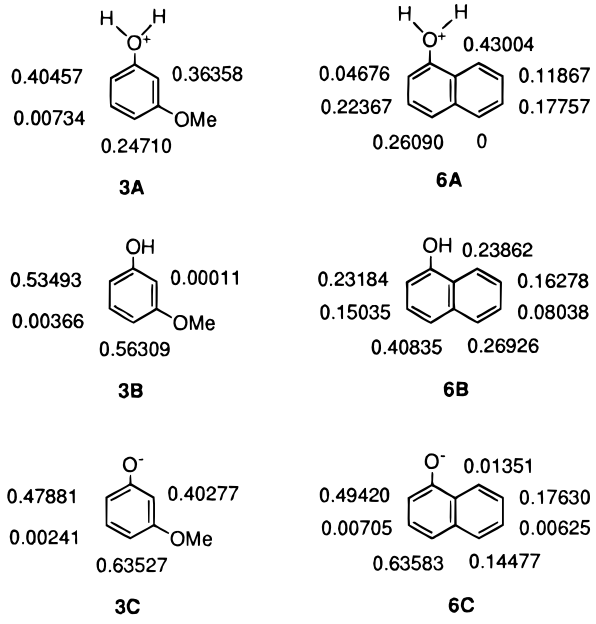


Figure 1. Selected electron densities in HOMOs of a protonated form **A**, a neutral form **B**, and a deprotonated form **C** of 3-methoxyphenol (**3**) and 1-naphthol (**6**).

A on the hydroxy (OH) group, neutral forms **B**, and deprotonated forms **C** were performed by the AM-1 method.[9] We investigated HOMOs because the phenolic substrates should act as nucleophiles in these nitrosation reactions (Figure 1). In neutral forms **B** and deprotonated forms **C** of substrates **3** and **6**, the highest electron density was on C_4 (*para*). In the protonated forms the highest electron density of **3A** was on C_6 (*ortho*), whereas the electron density on C_2 (*ortho*) of **6A** was quite low. An orbital-controlled process should contribute to electrophilic aromatic substitution with a noncationic species.[10] Thus, though additional factors must be taken into consideration in the nitrosation of phenolic compounds under acidic conditions, *para*-selectivity under the weakly basic conditions in method B is supported by the MO calculations.

Basic nitrosation using various phenolic substrates was further examined to establish the scope and limitations of the reaction (Table 2). Phenol itself (Table 2, run 1), *para*-unsubstituted phenols activated with electron-donating groups (EDGs) (Table 2, runs 2−4), and a halogenated phenol (Table 2, run 5) efficiently yielded the corresponding *p*-quinone monooximes. Phenols deactivated with electron-withdrawing groups (EWGs) such as salicylaldehyde (Table 2, run 6) and methyl salicylate (Table 2, run 7) also could be nitrosated under slightly vigorous conditions, but there was no nitrosation when a carboxyl group was substituted as an EWG (Table 2, run 8). Introducing a methoxy group to the *para* position of the carbonyl group of salicylaldehyde lowered the yield (Table 2, run 9), whereas more satisfactory results were obtained by introducing a methyl group into the same position of methyl salicylate (Table 2, run 10). Nitrosation was either ineffective or absent when a carbonyl group was located at the *meta* position of the OH group (Table 2, runs 11−13). Blocking the *para* position of the OH group by a methyl group caused nitrosation to fail (Table 2, run 15). The more reactive methoxy group led to nitrosation/oxidation[11] in which a nitro group was introduced into the *ortho* position of the OH group, but the yield was low (Table 2, run 14).

The basic nitrosation was further applied to naphthols and some phenolic heterocyclics. Nitrosation proceeded smoothly on 2-[12] (Table 2, run 16) and 3-aryl-1-naphthols[13] (Table 2, run 17) to give a single *para*-nitrosated product from each. The products were isolated after methylation in a one-pot reaction because of their relative instability during isolation. A benzofuran derivative was nitrosated to afford the desired product in moderate yield[14] (Table 2, run 18). On more electron-deficient heterocyclics, the smooth introduction of a nitrogen function occurred only when the *para* position of coumarin derivatives was unblocked (Table 2, runs 19 and 20). This basic nitrosation was also applicable to a quinoline derivative (Table 2, run 21).

A variety of phenolic substrates were nitrosated under mildly basic conditions to give quinone monooximes in moderate to high yields, when the *para* positions were

(8) The presence of a nitroso tautomer on the 2-nitrosated 1-naphthol **7** in solution was controversial. ^{1}H NMR studies showed that the ratio of tautomeric mixtures was dependent on the polarity of the solvent, namely an oxime/naphthol ratio of 2:1 in $CDCl_3$ and a 100% oxime population in DMSO-d_6, respectively. (Geraldes, C. F. G. C.; Silva, M. I. F. *Opt. Pura Apl.* **1988**, *21*, 71; *Chem. Abstr.* **1990**, *112*, 7140k.) An examination using ^{17}O NMR has supported the above findings, in which the absence of a nitroso tautomer was observed in a mixed solution of acetonitrile and acetone (1:3). (Dahn, H.; Pechy, P.; Flogel, R. *Helv. Chim. Acta* **1994**, *77*, 306.) We independently reconfirmed that **7** exists as tautomeric mixtures in $CDCl_3$ solution from the ^{1}H NMR spectra (see the Experimental Section).

(9) MO calculations were performed by the AM-1 method with CAChe ver. 3.6.

(10) Klopman, G. In *Chemical Reactivity and Reaction Paths*; Klopman, G., Eds; John Wiley: New York, 1974; pp 81−82.

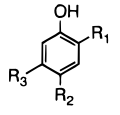
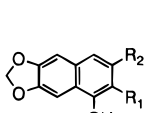
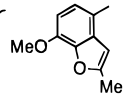
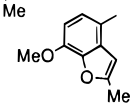
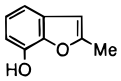
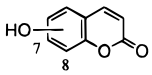
(11) In some reactive aromatic compounds, nitrous acid-catalyzed nitration has been reported.[1]

(12) Ishii, H.; Ishikawa, T.; Murota, M.; Aoki, Y.; Harayama, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1019.

(13) Preparation of this naphthol will be reported elswhere.

(14) An *ortho*-nitrated product, 7-hydroxy-2-methyl-6-nitrobenzo[*b*]-furan,[11] was formed in 11% yield as an additional product: yellow needles (from ethyl acetate−hexane); mp 124−126 °C; IR (cm^{-1}) 3422; ^{1}H NMR ($CDCl_3$) δ 2.56 (d, 3H, J = 1.0 Hz), 6.47 (q, 1H, J = 1.0 Hz), 7.03 (d, 1H, J = 8.8 Hz), 7.94 (d, 1H, J = 8.8 Hz), 11.18 (s, 1H). Anal. Calcd for $C_9H_7NO_4$: C, 55.96; H, 3.65; N, 7.25. Found: C, 56.04; H, 3.42; N, 7.12.

Table 2. Nitrosation of Various Phenolic Substrates under Basic Conditions (Method B)

run	substrate				*i*-$AmNO_2$ (Meq.)	K_2CO_3 (Meq.)	temp. (°C)	time (h)	*p*-quinone monooxime yield (%)[a]
	I. Phenols	R_1	R_2	R_3					
1		H	H	H	1.2	1.5	rt	24	88
2		OMe	H	H	1.2	1.5	rt	3	83
3		OBzl	H	H	1.2	1.5	rt	24	80[b]
4		Me	H	H	1.2	1.5	rt	12	66
5		Cl	H	H	1.2	1.5	rt	24	60
6		CHO	H	H	2.4	1.5	50	45	78
7		CO_2Me	H	H	2.4	1.5	50	41	42[c]
8		CO_2H	H	H	2.4	2.6	50	70	NR[d]
9		CHO	H	OMe	2.4	1.5	50	7	37
10		CO_2Me	H	Me	2.4	1.5	50	99	69
11		H	H	CO_2Me	2.4	1.5	50	45	NR[d]
12		OMe	H	CHO	1.2	1.5	50	45	NR[d]
13		OMe	H	CO_2H	2.4	2.6	50	18	NR[d]
14		H	OMe	H	1.2	1.5	rt	24	29[e]
15		H	Me	H	1.2	1.5	50	48	NR[d]
	II. Naphthols	R_1		R_2					
16				H	1.2	10	rt	6	80[b]
17		H			1.7	10	rt	3.5	77[b]
	III. Heterocycles								
18					1.2	1.5	rt	3	57[f]
19				8-OH	1.4	1.5	50	24	79
20				7-OH	2.5	1.5	50	24	NR[d]
21					1.1	1.5	50	4	71

[a]Nonoptimized, isolated yield. [b]Isolated as a methyl ether. [c]Starting material was recovered. [d]No reaction. [e]The product was 4-methoxy-2-nitrophenol. [f]An *ortho*-nitrated product was concomitantly obtained in 11 % yield.

not blocked.[15] Phenols activated by an EDG react faster than phenols deactivated by an EWG. Under the latter conditions, the successful reactions were limited to phenols in which the carbonyl function is located at the *ortho* position of the OH group. The reaction also proceeded smoothly in bicyclic fused phenolic systems.

The ^{1}H NMR spectra of *p*-quinone monooximes derived from bicyclic phenolic compounds were occasionally complex. Products from the 2-aryl-1-naphthol (Table 2, run 16) and the benzofuran (Table 2, run 18) were composed of *E* and *Z* isomers in a ratio of 4:1 and 6:1, respectively. On the other hand, the products from 1-naphthol (**6**) itself (Table 1, run 2), the 3-aryl-1-naphthol (Table 2, run 17), the coumarin (Table 2, run 19), and the quinoline[16] (Table 2, run 21) were single isomers. Thus, the ratio of geometric isomers in the product should depend upon their structural features.

Futhermore, the corresponding oxime ethers were produced in high yield by successive alkylation in a one-pot operation without isolating the nitrosated products as described.[4]

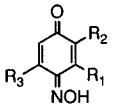
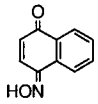
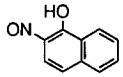
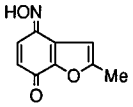
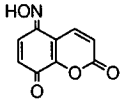
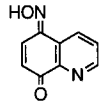
Although diazo coupling results in a C−N bond in phenols under basic conditions, the basic nitrosation reaction is, to our knowledge, the first example of a practical C−N bond formed in phenols by direct electrophilic aromatic substitution under mildly basic condition. Therefore, the reaction described here should provide a promising synthetic procedure for the regioselective preparation of *p*-quinone monooximes and their ethers from phenols.[17]

Antiviral Activity. We tested the antiviral activities of some nitrosated products against HSV-1, HSV-2, and HIV-1. Acyclovir (ACV) was used as a control in the HSV

(15) Nonphenolic substrates such as 1,3-dimethoxybenzene or *N*,*N*-diethylaniline were not nitrosated. Furthermore, a trial for nitration using isoamyl nitrate (*i*-$AmNO_3$), instead of *i*-$AmNO_2$, under the conditions of basic nitrosation resulted in complete recovery of the starting material.

(16) A simple signal pattern due to a single product was observed in the ^{1}H NMR spectrum when the crude quinone monooxime was purified by silica gel column chromatography (see the Experimental Section), whereas the product obtained by either recrystallization or alumina column chromatography showed the presence of a pair of geometrical isomers in a ratio of 3:1 under the same conditions: ^{1}H NMR (DMSO-d_6) δ 6.15 (d, 3/4 × 1H, J = 9.8 Hz), 6.42 (d, 1/4 × 1H, J = 9.8 Hz), 7.19 (d, 3/4 × 1H, J = 9.8 Hz), 7.52 (dd, 1/4 × 1H, J = 8.5, 4.2 Hz), 7.54 (dd, 3/4 × 1H, J = 8.5, 4.2 Hz), 8.19 (d, 1/4 × 1H, J = 9.8 Hz), 8.60 (dd, 1/4 × 1H, J = 4.2, 1.7 Hz), 8.62 (dd, 3/4 × 1H, J = 4.2, 1.7 Hz), 9.29 (dd, 3/4 × 1H, J = 8.5, 1.7 Hz), 9.83 (dd, 1/4 × 1H, J = 8.5, 1.7 Hz).

Table 3. Antiviral Activities of Some Nitrosated Products

run	substrate	HSV systems[a] HSV-1 EC_{50} (μg/mL)	HSV systems[a] HSV-2 EC_{50} (μg/mL)	HIV-1[b] EC_{50} (μg/mL)
	R_1 R_2 R_3			
1	 OMe H H	3.2	inactive[c]	inactive[c]
2	H CHO H	inactive[c]	inactive[c]	inactive[c]
3	H CO_2Me H	inactive[c]	inactive[c]	0.32
4	H CHO OMe	inactive[c]	inactive[c]	inactive[c]
5	H CO_2Me Me	inactive[c]	inactive[c]	inactive[c]
6		inactive[c]	inactive[c]	0.32
7		inactive[c]	inactive[c]	inactive[c]
8		inactive[c]	inactive[c]	0.32
9		inactive[c]	inactive[c]	0.32
10		2.7	3.4	inactive[c]
controls	ACV	0.27-0.47	0.40-0.47	——
	DDI	——	——	0.46-1.0
	AZT	——	——	0.0032

[a]Plaque reduction assays for HSV-1 (strain KOS) and HSV-2 (strain 186) were performed using Vero cell monolayers as described[18] with a slight modification. Inhibition of plaque development for both viruses was evaluated on monolayers after a 1 to 2 day incubation at 37 °C. EC_{50} values were determined from the drug concentration that conferred 50 % plaque reduction compared to virus controls. [b]Indirect immunofluorescence assay for HIV-1 (strain III_B) was performed with MT-4 cells by the reported procedure.[19] Briefly, MT-4 cells were infected with HIV-1 in the presence of various concentrations of test compounds. After a 4 day incubation at 37 °C, HIV-1 positive MT-4 cells were detected by an indirect immunofluorescence method. EC_{50} values were determined from the drug concentration that reduced the percentage of HIV-1 antigen-positive MT-4 cells to 50 % compared with virus controls. [c]The antiviral activity was not observed at the range of dose without cytotoxicity.

system,[18] and dideoxyinosine (DDI) and azidothymidine (AZT) were used in the HIV system.[19] Although the antiviral assay was done in a single experiment, highly reproducible results are obtained in plaque reduction assay for the former system and indirect immunofluorescence assay for the latter system compared to the other method, *e.g.*, the cytopathic effect method, in our experience (Table 3). Two *p*-quinone monooximes derived from 3-methoxyphenol (Table 3, run 1) and 8-hydroxyquinoline (Table 3, run 10) showed moderate activity against HSV-1. The latter oxime was also effective against HSV-2.

These anti HSV-active quinone monooximes were inactive against HIV-1. Activity comparable to that of DDI against HIV-1 was shown by a simple *p*-quinone monooxime derived from methyl salicylate (Table 3, run 3) and *p*-quinone monooximes with a fused ring system such as naphthalene (Table 3, run 6), benzofuran (Table 3, run 8), and coumarin (Table 3, run 9) skeletons.

A comparison between both nitrosated products from 1-naphthol (Table 3, runs 6 and 7) indicated that a *p*-quinone monoxime structure is more crucial than a nitroso form for anti HIV-1 activity because of the inactivity of 2-nitrosated 1-naphthol. We found that a natural 1,4-naphthoquinone derivative has moderate activities against HSV-1 and HSV-2, but none against HIV-1.[20] These findings support the notion that the partial oxime moiety of 1,4-naphthoquinone monooxime plays an important role in anti-HIV-1 activity. In addition, the planarity of a compound may be an alternative factor in anti-HIV-1 activity because bicyclic quinone monooximes were usually effective.

Thus, a *p*-quinone monooxime structure may be a fundamental unit for antiviral activities, and more planar

(17) The Baudisch reaction, in which a chelate structure could govern the orientation of substitution, is used for the regioselective introduction of a nitroso group into the *ortho* position of the OH group in phenols. (a) Cronheim, G. *J. Org. Chem.* **1947**, *12*, 7. (b) Cone, M. C.; Melville, C. R.; Carney, J. R.; Gore, M. P.; Gould, S. J. *Tetrahedron* **1995**, *51*, 3095.

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bicyclic *p*-quinone monooximes may be potent anti-HIV-1 agents.

Experimental Section

General. Melting points are uncorrected. IR spectra were obtained in Nujol. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded with tetramethylsilane as the internal reference. Columns for chromatography contained silica gel 60 (70−230 mesh ASTM; Merck), and TLC proceeded on silica gel GF_{254} (Merck). In general, the extract was washed with brine, dried over magnesium sulfate, and filtered. The filtrate was evaporated to dryness under reduced pressure. Acidic nitrosation (method A) proceeded as described.[6]

General Procedure for Basic Nitrosation of Phenols (Method B). As described previously,[4] *i*-$AmNO_2$ (1.2−1.4 equiv) was added to a stirred 0.1 M solution of a phenol (1 equiv) in DMF in the presence of K_2CO_3 (1.5−2.6 equiv) at 0 °C under argon. The reaction mixture was stirred at room temperature until the starting material disappeared on TLC and then diluted with water and extracted with ethyl acetate. Recrystallization of the crude product from an appropriate solvent gave a *p*-quinone monooxime. The products were also separated or purified by means of column chromatography.

On 3-Methoxyphenol (3) (Table 1, Run 1). Column chromatography using ethyl acetate−hexane (1:1) afforded two products. **(a) 5-Methoxy-2-nitrosophenol (4)**: a less polar component; reddish brown needles; mp 152−156 °C dec (lit.[6] mp 153−154 °C). **(b) 2-Methoxy-1,4-benzoquinone 1-oxime (5)**: a more polar component; reddish brown needles; mp 183−185 °C dec (lit.[21] mp 174 °C).

On 1-Naphthol (6) (Table 1, Run 2). Column chromatography using ethyl acetate−hexane (1:1) afforded two products. **(a) 2-Nitroso-1-naphthol (7)**: a more polar component; reddish brown needles; mp 155−160 °C dec (lit.[3] mp 142−146 °C); ^{1}H NMR ($CDCl_3$) δ 6.90 (d, 1H, J = 9.8 Hz), 6.96 (d, 5/9 × 1H, J = 9.8 Hz), 7.25 (d, 4/9 × 1H, J = 9.8 Hz), 7.36 (d, 4/9 × 1H, J = 7.8 Hz), 7.41 (t, 4/9 × 1H, J = 7.8 Hz), 7.47 (d, 5/9 × 1H, J = 7.8 Hz), 7.49 (dt, 5/9 × 1H, J = 7.8, 1.2 Hz), 7.59 (t, 4/9 × 1H, J = 7.8 Hz), 7.72 (dt, 5/9 × 1H, J = 7.8, 1.2 Hz), 8.20 (d, 4/9 × 1H, J = 7.8 Hz), 8.35 (dd, 5/9 × 1H, J = 7.8, 1.2 Hz). **(b) 1,4-Naphthoquinone 1-oxime (8)**: a less polar component; light brown needles; mp 206−208 °C dec (lit.[3] mp 197 °C); ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 6.63 (d, 1H, J = 10 Hz), 7.53 (ddd, 1H, J = 8.7, 7.2, 1.4 Hz), 7.63 (ddd, 1H, J = 8.7, 7.2, 1.4 Hz), 8.03 (d, 1H, J = 10 Hz), 8.15 (dd, 1H, J = 7.2, 1.4 Hz), 8.23 (dd, 1H, J = 7.2, 1.4 Hz).

On Phenol: 1,4-Benzoquinone 1-Oxime (Table 2, Run 1). Recrystallization from ethyl acetate−hexane gave reddish brown needles: mp 140−143 °C (softened at 130 °C) dec (lit.[22] mp 126−128 °C).

On 2-Methoxyphenol: 3-Methoxy-1,4-benzoquinone 1-Oxime (Table 2, Run 2). Recrystallization from ethyl acetate−hexane gave reddish brown prisms: mp 179−181 °C (lit.[22] mp 176−177 °C).

On *o*-Cresol: 3-Methyl-1,4-benzoquinone 1-Oxime (Table 2, Run 4). Recrystallization from ethyl acetate−hexane gave orange prisms: mp 138−140 °C dec (lit.[22] mp 134−135 °C).

On 2-Chlorophenol: 3-Chloro-1,4-benzoquinone 1-Oxime (Table 2, Run 5). Recrystallization from ethyl acetate−hexane gave reddish needles: mp 143−146 °C dec (lit.[22] mp 147−148 °C).

On Salicylaldehyde: 3-Formyl-1,4-benzoquinone 1-Oxime (Table 2, Run 6). Recrystallization from ethyl acetate−hexane gave labile reddish brown prisms: mp 110−114 °C (softened at 102 °C) dec; IR (cm^{-1}) 3160, 1661; ^{1}H NMR ($CDCl_3$) δ 7.11 (d, 1H, J = 9.0 Hz), 7.78 (d, 1H, J = 9.0 Hz), 8.61 (s, 1H), 10.14 (s, 1H), 11.80 (s, 1H); HRMS calcd for $C_7H_5NO_3$ 151.0269, found 151.0255.

On Methyl Salicylate: 3-(Methoxylcarbonyl)-1,4-benzoquinone 1-Oxime (Table 2, Run 7). Recrystallization from hexane gave slightly green needles: mp 93−96 °C (lit.[23] mp 89−90 °C).

On 4-Methoxysalicylaldehyde: 2-Methoxy-5-formyl-1,4-benzoquinone 1-Oxime (Table 2, Run 9). Column chromatography using $CHCl_3$−MeOH (10:1) gave a labile dark red amorphous mass: IR (cm^{-1}) 3432, 1711, 1655; ^{1}H NMR ($CDCl_3$) δ 4.30 (s, 3H), 6.74 (s, 1H), 6.75 (s, 1H), 9.76 (s, 1H), 11.91 (s, 1H); HRFABMS calcd for $C_8H_8NO_4$ 182.0453, found 182.0454.

On Methyl 4-Methylsalicylate: 5-(Methoxycarbonyl)-2-methyl-1,4-benzoquinone 1-Monooxime (Table 2, Run 10). Recrystallization from EtOH gave slightly green needles: mp 90−93 °C; IR (cm^{-1}) 3163, 1685; ^{1}H NMR ($CDCl_3$) δ 3.28 (s, 3H), 3.96 (s, 3H), 7.04 (s, 1H), 7.05 (s, 1H), 11.37 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.12, 52.80, 109.55, 111.97, 119.84, 150.10, 161.43, 166.87, 170.71. Anal. Calcd for $C_9H_5NO_4$: C, 55.39; H, 4.65; N, 7.18. Found: C, 55.38; H, 4.44; N, 7.15.

On 4-Methoxyphenol: 4-Methoxy-2-nitrophenol (Table 2, Run 14). Column chromatography using ethyl acetate−hexane (1:4) gave yellow needles: mp 69−71 °C (lit.[24] mp 80 °C); IR (cm^{-1}) 3234; ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H), 7.09 (d, 1H, J = 9.0 Hz), 7.22 (dd, 1H, J = 9.0, 3.1 Hz), 7.51 (d, 1H, J = 3.1 Hz), 10.35 (s, 1H). Anal. Calcd for $C_7H_7NO_4$: C, 49.71; H, 4.17; N, 8.28. Found: C, 49.51; H, 4.06; N, 8.00.

On 7-Hydroxy-2-methylbenzo[*b*]furan:[25] 2-Methyl-4,7-benzo[*b*]furanoquinone 4-Oxime (Table 2, Run 18). Recrystallization from ethyl acetate−hexane gave dark red prisms: mp 195−198 °C dec; IR (cm^{-1}) 3162, 1626; ^{1}H NMR (DMSO-d_6) δ 2.44 (s, 1/7 × 3H), 2.45 (s, 6/7 × 3H), 6.41 (d, 1/7 × 1H, J = 10.2 Hz), 6.45 (d, 6/7 × 1H, J = 10.2 Hz), 6.68 (s, 1/7 × 1H), 7.01 (s, 6/7 × 1H), 7.28 (d, 6/7 × 1H, J = 10.2 Hz), 7.65 (d, 1/7 × 1H, J = 10.2 Hz). Anal. Calcd for $C_9H_7NO_3$: C, 61.02; H, 3.98; N, 7.91. Found: C, 60.73; H, 3.80; N, 7.76.

On 8-Hydroxycoumarin:[26] 5,8-Coumarinoquinone 5-Oxime (Table 2, Run 19). Recrystallization from ethyl acetate−hexane gave red prisms: mp 258−262 °C dec; IR (cm^{-1}) 3170, 3088, 1693, 1649; ^{1}H NMR (DMSO-d_6) δ 6.68 (d, 1H, J = 10.0 Hz), 6.76 (d, 1H, J = 10.0 Hz), 7.85 (d, J = 10.0 Hz), 8.16 (d, 1H, J = 10.0 Hz); ^{13}C NMR (DMSO-d_6) δ 118.51, 120.91, 123.39, 130.68, 138.21, 144.37, 147.13, 158.71, 176.76. Anal. Calcd for $C_9H_5NO_4$: C, 56.55; H, 2.64; N, 7.33. Found: C, 56.65; H, 2.49; N, 7.17.

On 8-Hydroxyquinoline: 5,8-Quinolinoquinone 5-Oxime (Table 2, Run 21). After completion of the reaction the DMF was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography with MeOH to give brown prisms: mp > 300 °C; IR (cm^{-1}) 1658; ^{1}H NMR (DMSO-d_6) δ 6.66 (d, 1H, J = 10.0 Hz), 7.73 (dd, 1H, J = 8.0, 4.4 Hz), 7.82 (d, 1H, J = 10.0, Hz), 8.80 (br d, 1H, J = 10.0 Hz), 8.88 (dd, 1H, J = 4.4, 1.3 Hz); HRFABMS calcd for $C_9H_7N_2O_2$ 175.0508, found 175.0501. Anal. Calcd for $C_9H_6N_2O_2 \cdot 1/10H_2O$: C, 61.43; H, 3.55; N, 15.92. Found: C, 61.31; H, 3.51; N, 15.59.

Preparation of *p*-Quinone Monooxime Methyl Ethers. As described previously,[4] *i*-$AmNO_2$ (1.2 equiv) was added to a stirred 0.1 M solution of a phenol (1 equiv) in DMF in the presence of K_2CO_3 (5−10 equiv) at 0 °C under argon. After the reaction mixture was stirred at room temperature until the starting material disappeared from TLC, dimethyl sulfate (Me_2SO_4) (1.1−1.4 equiv) was added at 0 °C, then the mixture was stirred at the same temperature for 1 h. After decomposition of the excess Me_2SO_4, *p*-quinone monooxime methyl ethers were purified by either recrystallization or column chromatography.

On 2-(Benzyloxy)phenol: 3-(Benzyloxy)-1,4-benzoquinone 1-Oxime Methyl Ether (Table 2, Run 3). Recrys-

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tallization from ethyl acetate−hexane gave reddish brown needles: mp 99−101 °C; IR (cm^{-1}) 3364, 3048; ^1H NMR ($CDCl_3$) δ 4.15 (s, 3H), 5.06 (s, 2H), 6.52 (d, 1H, J = 9.8 Hz), 6.78 (d, 1H, J = 2.5 Hz), 7.10 (dd, 1H, J = 9.8, 2.5 Hz), 7.32−7.43 (m, 5H). Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.78; H, 5.33; N, 5.67.

On 2-[4-(7-Methoxy-2-methylbenzo[*b*]furanyl)]-6,7-(methylenedioxy)-1-naphthol: 3-[4-(7-Methoxy-2-methylbenzo[*b*]furanyl)]-6,7-(methylenedioxy)-1,4-naphthoquinone 1-Oxime Methyl Ether (Table 2, Run 16). Recrystallization from MeOH−$CHCl_3$ gave reddish brown needles: mp 264−266 °C; IR (cm^{-1}) 1641; ^1H NMR ($CDCl_3$) δ 2.47 (s, 3H), 4.04 (s, 3H), 4.19 (s, 4/5 × 3H), 4.27 (s, 1/5 × 3H), 6.09 (s, 4/5 × 2H), 6.13 (s, 1/5 × 2H), 6.33 (s, 1H), 6.79 (d, 1H, J = 8.3 Hz), 7.25 (d, 1H, J = 8.3 Hz), 7.34 (s, 1/5 × 1H), 7.63 (s, 4/5 × 1H), 7.65 (s, 4/5 × 1H), 7.79 (s, 1/5 × 1H), 7.90 (s, 4/5 × 1H), 8.42 (s, 1/5 × 1H); HRFABMS calcd for $C_{22}H_{18}NO_6$ 392.1134, found 392.1125. Anal. Calcd for $C_{22}H_{17}NO_6 \cdot 1/10CHCl_3$: C, 65.81; H, 4.27; N, 3.47. Found: C, 66.19; H, 4.18; N, 3.37.

On 3-[4-(7-Methoxy-2-methylbenzo[*b*]furanyl)]-6,7-(methylenedioxy)-1-naphthol: 2-[4-(7-Methoxy-2-methylbenzo[*b*]furanyl)]-6,7-(methylenedioxy)-1,4-naphthoquinone 1-Oxime Methyl Ether (Table 2, Run 17). Recrystallization from CH_2Cl_2−hexane gave yellow prisms: mp 232−236 °C; IR (cm^{-1}) 1636; ^1H NMR ($CDCl_3$) δ 2.47 (s, 3H), 4.03 (s, 3H), 4.05 (s, 3H), 6.13 (s, 2H), 6.36 (s, 1H), 6.67 (s, 1H), 6.78 (d, 1H, J = 8.3 Hz), 7.20 (d, 1H, J = 8.3 Hz), 7.71 (s, 1H), 8.39 (s, 1H). Anal. Calcd for $C_{22}H_{17}NO_6$: C, 67.52; H, 4.38; N, 3.58. Found: C, 67.16; H, 4.17; N, 3.46.

Acknowledgment. We thank Mr. Toshiaki Saito, Showa College of Pharmacy, for the MO calculation. We also thank Dr. Takemitsu Nagahata and Ryuji Ikeda of Nippon Kayaku Co., Ltd., for assessing the antiviral activities.

Supporting Information Available: Copies of ^1H NMR spectra of all compounds and ^{13}C NMR spectra of nitrosated products of 3-methoxyphenol, 1-naphthol, methyl salicylate, methyl 4-methylsalicylate, and 8-hydroxycoumarin (27 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering informaton.

JO951873S